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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,705	06/14/2007	Shin-ichi Hashimoto	00005.001301.	8726

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EXAMINER	
MEAH, MOHAMMAD Y	
ART UNIT	PAPER NUMBER
1652	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,705	HASHIMOTO ET AL.	
	Examiner	Art Unit	
	MD. YOUNUS MEAH	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-15 were examined in the previous action.

Claims 1-3, 5-15 are currently pending in the instant application. In response to a previous office action, a non-final action (mailed on 8/5/2008), applicants on 12/30/08 cancel claims 4 and 16-26. Applicants' response on 12/30/08 is acknowledged.

Claims 1-3, 5-15 are under consideration.

Applicants' arguments filed on 12/30/08 have been fully considered but they are found unpersuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Objection

Claim 7 is objected to for reciting "possessed by", the term "possessed by" should be replaced with "comprised in". Appropriate correction is required.

Claim 9 is objected to for reciting "is introduced belongs to", the term "is introduced belongs to" should be replaced with "is introduced". Appropriate correction is required.

Claim 10 is objected to for reciting "is introduced belongs to", the term "is introduced belongs to" should be replaced with "is introduced". Appropriate correction is required.

Claim 11 is objected to for reciting "is introduced belongs to", the term "is introduced belongs to" should be replaced with "is introduced". Appropriate correction is required.

Claim 12 is objected to for reciting "is introduced is selected from the group", the term "is introduced is selected from the group" should be replaced with "is introduced selected from the group". Appropriate correction is required.

Claim 13 is objected to for reciting "is introduced belongs to", the term "is introduced belongs to" should be replaced with "is introduced is".

Appropriate correction is required.

Claim 14 is objected to for reciting "L-triptophan" and "L-thyrosine", the terms "L-triptophan" and "L-thyrosine"" should be replaced with "L-tryptophan" and "L-tyrosine". Appropriate correction is required.

Claim Rejections

35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all

Obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 6, 8-9, 14 and15 are rejected under 35 U.S.C. 103(a) by Bott *et al* (*J. Biotechnol*, 2003, 129-153, from IDS) in view of Molenaar *et al* (J. *Bactorl*, 2000, 6884-6891, from IDS), Hollander *et al* (*Appl Micriobiol Biotechnol* 1994, 42, 508-515) and Nakagawa *et al* (US20020197605).

Bott *et al* describes the production of amino acids, such as, glutamate and L-lysine (page 130 left column, 1st pargh) by *Corynebacterium glutamicum* and that respiratory chain enzymes involved in the oxidative phosphorylation in the aerobic respiration of *Corynebacterium glutamicum* are useful in amino-acid production and one such enzyme is NADH dehydrogenase (abstract and FIG 1). However; Bott *et al* do not teach the method of producing amino acid by using microorganism transformed with heterologous type-II NADH dehydrogenase derived from *Corynebacterium glutamicum*.

Molenaar *et al* teach NADH dehydrogenase gene of SEQ ID NO: 1 encoding NADH dehydrogenase (100% identical to applicants SEQ ID NO: 4) isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH dehydrogenase gene of SEQ ID NO: 3 and Molenaar *et al* teach said NADH dehydrogenase is Type II NADH, wherein in the reaction number of proton discharged per electron is zero (page 6884, right column last pargh). Molenaar *et al.* also teach that *Corynebacterium glutamicum* comprise said type II NADH dehydrogenase is the only membrane bound NADH dehydrogenase; since disruption of said NDH gene had

completely lost membrane bound NADH dehydrogenase activity (page 6887, right column 1st paragraph).

Methods of expressing endogenous and exogenous genes in a host cell are well known in art to enhance the production of proteins and small organic compound. For example, Nakagawa *et al* teach an improved production of fine chemicals, such as, amino acid, and vitamins, by using a production strain of transformed host cell such as *E. coli* (subject matter of claims 8-9) with exogenous gene encoding desired enzymatic activities (page 7 parghs 0179-0191; page 14, pargh 0312-0313). Amino acids such as, L-lysine is industrially important chemicals.

It is well known in art that NADH is produced in several reactions in the amino acid biosynthesis pathway of *Corynebacterium glutamicum* (Hollander *et al. Appl Micriobiol Biotechnol* 1994, 42, 508-515, Fig 1 at page 509). NADH dehydrogenase converts NADH to NAD. Hollander *et al* teach that quantitative yield of lysine can be produced from glucose in a fermentation system comprising *Corynebacterium,* if NADH and NADPH are consumed (its concentration is decreased) (last pargh, page 514). Therefore, since type-II membrane bound NADH dehydrogenase of *Corynebacterium glutamicum* converts NADH to NAD, by doing so it depletes the NADH and increase the production of lysine from glucose. Therefore, in order to produce amino acid in large scale, one of ordinary skill in the art is **motivated** to express *E.coli* (as taught Nakagawa *et al*) with NADH dehydrogenase gene of SEQ ID NO: 1 (encoding Type-II membrane bound NADH dehydrogenase) of *Corynebacterium glutamicum* of Molenaar

et al and use the said transformed microorganism in the method of production of amino acid.

As such it would have been obvious to one of ordinary skill in the art to use Molenaar *et al* NADH gene of SEQ ID NO: 1 encoding a type II NADH dehydrogenase (which discharge zero proton per electron) isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH gene of SEQ ID NO: 3 express the said gene in *E. coli* and use the transformed E. *coli* to the method of production of amino acid.

Claims 5 and 7 are rejected under 35 U.S.C. 103(a) by Bott *et al* (*J. Biotechnol*, 2003, 129-153, from IDS) in view of Molenaar *et al* (J. *Bactorl.*, 2000, 6884-6891), Hollander *et al* (*Appl Micriobiol. Biotechnol.* 1994, 42, 508-515) and Nakagawa *et al* (US20020197605).

The teaching of Bott *et al*, Hollander *et al* and Nakagawa *et al* is discussed above for the 35 U.S.C. 103(a) rejection of claims 1-3, 6, 8-9, 14-15. However Bott *et al*, Hollander *et al* and Nakagawa *et al* do not teach explicitly process of producing amino acid using *E. coli* DH5α/pCS-CGndh strain.

Since Molenaar *et al* teach NADH gene of SEQ ID NO: 1, encoding Type II NADH dehydrogenase isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH gene of SEQ ID NO: 3, and since *E. coli* DH5α strain is known in prior art, one ordinary skill in the art would use Molenaar *et al* NADH gene of SEQ ID NO: 1 express in a known vector (specific vector used by the applicant is known in prior art, page 39 of the specification) and make a plasmid and introduce said

plasmid in *E. coli* DH5α strain. One ordinary skill in the art would do so because of the motivation, as explained above in the 35 U.S.C. 103(a) rejection of claims 1-3, 5-15, and prior art teach the embodiments comprising the gene, expressing the gene in a vector and making a plasmid and also teach the *E. coli* DH5α strain.

As such it would have been obvious to one of ordinary skill in the art to use Molenaar *et al* NADH gene of SEQ ID NO: 1, encoding type II NADH dehydrogenase isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH gene of SEQ ID NO: 3 and express the said gene in *E. coli* DH5α strain and use the transformed *E. coli* DH5α strain to the method of production of amino acid, such as L-lysine.

Claims 11-13 are rejected under 35 U.S.C. 103(a) by Bott *et al* (*J. Biotechnol*, 2003, 129-153, from IDS) in view of Molenaar *et al* (J. *Bactorl*, 2000, 6884-6891), Hollander *et al* (*Appl Micriobiol. Biotechnol*. 1994, 42, 508-515) and Nakagawa *et al* (US20020197605).

The teaching of Bott *et al*, Hollander *et al* and Nakagawa *et al* is discussed above for the 35 U.S.C. 103(a) rejection of claims 1-3, 6, 8-9, 14-15. However Bott *et al*, Hollander *et al* and Nakagawa *et al* do not teach explicitly process of producing amino acid using *Corynebacterium glutamicum* expressing heterologous NADH-II dehydrogenase gene of SEQ ID NO: 1.

Since Bott *et al* describes the production of amino acids by *Corynebacterium glutamicum* in the biosynthesis of amino acids use different respiratory chain enzymes and one of the enzymes used is NADH dehydrogenase (NADH-II), in order to further

enhance the production of amino acids by *Corynebacterium*, one ordinary skill in the art is motivated to express heterologous NADH-II dehydrogenase gene of SEQ ID NO: 1 of Molenaar *et al*.) in *Corynebacterium or Corynebacterium glutamicum*. One of ordinary skill in the art would reasonably expect this to increase the amount of the NADH-II dehydrogenase produced in the *Corynebacerium* and therefore, enhance the amino acid production.

As such it would have been obvious to one of ordinary skill in the art to use Molenaar *et al* NADH dehydrogenase gene of SEQ ID NO: 1 encoding type II NADH dehydrogenase isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH gene of SEQ ID NO: 3 express the said gene in *corynebacterium or Corynebacterium glutamicum* and use the transformed *Corynebacterium* or *Corynebacterium glutamicum* to the method of production of amino acid, as taught by Bott *et al*.

Arguments and response

Applicants' argue, at page 10-11 of their amendment of 12/30/08, that Bott *et al* describe qualitative changes of the respiratory chain enzymes (such as, NADH dehydrogenase) for amino acid production and does not teach what the change is and further refer to another prior art Nakai *et al* (US2002/0160461) showing that mutation of energy non-producing NADH in *E. coli* does not effect the amino acid production in *E. coli*. Applicants' argue that one of ordinary skill in the art would not introduce Type II NADH dehydrogenase gene Molenaar *et* isolated from *Corynebacterium glutamicum*

which is 100% identical to applicant NADH gene of SEQ ID NO: 3 to microorganism for the production of amino acid.

Applicants' arguments files on 12/30/08 have been fully considered, but they found unpersuasive. Two type of NADH dehydrogenases (NADH-I, energy producing and NADH-II energy non-producing) describe in bacteria (see Bott *et al* page 331, section 3.1). As discussed above *Corynebacterium glutamicum* is amino acid producing microorganism having only type II NADH dehydrogenase, wherein in the reaction number of proton discharged per electron is zero (taught by Molenaar *et al*). Type II NADH dehydrogenase is involve as a primary dehydrogenase, linked with central metabolism, in the respiratory chain of *Corynebacterium glutamicum* and its growth and for the production of amino acid. One of ordinary skill in the art recognizes that energy non-producing type II NADH dehydrogenase is involved in amino acid production in *Corynebacterium glutamicum.* Regarding Nakai *et al* (US2002/0160461), *E. coli,* in Nakai *et al's*, could use other NADH dehydrogenase (NADH I), because *E. coli* contains NADH-I, for the production of amino acid. As explained above since *Corynebacterium glutamicum* uses type-II NADH dehydrogenase in amino acid biosynthesis, one ordinary skill in the art would introduce Molenaar *et al* NADH gene of SEQ ID NO: 1 isolated from *Corynebacterium glutamicum* which is 100% identical to applicant NADH gene of SEQ ID NO: 3 to a microorganism to enhance the production of amino acid. Thus, the claimed invention remains *prima fasciae* obvious over the prior art of record.

Allowable Subject Matter/Conclusion

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, NASHAAT T NASHED can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Mohammad Younus Meah
Examiner, Art Unit 1652

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